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(54) Title: SKIN PHOTOAGEING AND ACTINIC DAMAGE TREATMENT

(57) Abstract: Use of equol, dehydroequol, and other isoflav-3-enes are described for the prevention and/or treatment of skin photoageing and actinic damage. Methods of treating these conditions are also described.

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SKIN PHOTOAGEING AND ACTINIC DAMAGE TREATMENT

Field of the Invention

The present invention relates to the use of equol and dehydroequol in particular, and compounds based on an isoflavonoid ring structure in general for the prevention and/or treatment of skin photoageing and actinic damage.

Background

DNA damage in skin cells is particularly important to human health because it can have major effects on skin appearance and well-being, in particular skin carcinogenesis. DNA damage occurs when the ultraviolet (UV) light component (particularly UV-B and UV-C) of sunlight passes through to the lower layers of the epidermis. In its passage through the epidermis, the UV irradiation causes mutations in the DNA strands in the genomes of all cells in the skin. Those mutations are known as pyrimidine dimers which normally are repaired automatically by specialist intra-nuclear enzymes such as endonucleases, with complete repair taking about 2-3 days. Repair involves the excision of the damaged segment and insertion of a new segment. DNA damage caused by UV-induced oxidative stress, which following a complex lengthy cascade resulting in the generation of reactive oxygen species (ROS), takes up to 3 days to occur.

This DNA damage has a number of potentially damaging consequences, particularly where the sunlight exposure is repeated and occurs over many years. These include a small proportion of dimers being mis-repaired, predisposing to mutagenic damage, in particular if the mis-repair occurs in important quality assurance genes such as p53. The accumulation of these mis-repaired genes over a lifetime believed to be a major predisposing factor to skin cancer.

The consequences of UV-induced DNA damage in skin, or other UV-induced skin damage may be associated with photoageing, actinic damage and carcinogenesis. These terms generally have the following meaning:

1. Photoageing refers to the process of accelerated ageing in sunlight-exposed skin. This embraces fine lines and wrinkles, freckles, yellowing of the skin, stretching, dilated capillaries (*telangiectasis*), cherry red spots (*angiomas*), and a dry complexion.

2. Actinic damage refers to pre-malignant or benign skin growths and embraces lesions such as solar keratoses or actinic keratoses.

3. Skin cancer refers to lesions with malignant potential and includes basal cell carcinoma, Bowen's disease (in situ squamous cell carcinoma), squamous cell carcinoma and melanoma.

The use of anti-inflammatory agents, skin rehydration, collagen injections, surgery and dermabrasion are just some of the many cosmetic products and procedures employed in attempts to redress the consequences of photoageing, and actinic damage.

A strategy that was able to promote DNA protection and/or repair would have several important benefits. First, by reducing the time to effect DNA repair, the pathological consequences would be reduced. Second, the repair process would be more efficient with less likelihood of mis-repairs occurring. The benefit of this strategy is confirmed by the use of topical administration of endonucleases in patients with the genetic disorder, xeroderma pigmentosus. Individuals with this condition fail to make endonucleases, the consequence of which is a high risk of malignant skin cancer and photoageing of skin following sunlight exposure. The application to the skin of these individuals of exogenous endonucleases significantly reduces the risk of these individuals to skin cancer and address photoageing. Thirdly, by increasing the production of free radical scavengers in the skin, DNA would be protected from oxidative stress lesions that form in response to UV exposure.

It has been speculated that certain compounds, including equol, may have the ability to prevent the onset of some symptoms of ageing in skin (US Patent 6,060,070, Gorbach).

The Gorbach patent is concerned with the natural process of ageing that is associated with all tissues in the body and may be associated with reduced estrogen function with advancing age. Lowered collagen content and reduced numbers of elastin fibres in skin as a consequence of falling estrogen levels are though to be the primary factors causing age-related wrinkles. Normal ageing is a distinctive entity to photoageing.

It has now been found by the applicants that compounds of the present invention, namely equol, dehydroequol and other isoflav-3-ene and isoflavan compounds, when applied to the skin or administered orally or parenterally, surprisingly promote repair of pyrimidine dimers and reduce oxidative stress lesions in skin. It was entirely unexpected that the compounds of the present invention promoted DNA repair, and even more surprising to find that they promoted DNA repair and protection, and could be used to prevent and/or treat skin photoageing and actinic damage.

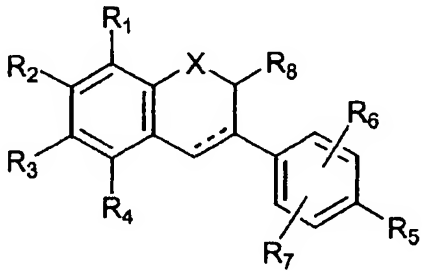
In accordance with a first aspect of this invention there is provided use of equol, dehydroequol, or other isoflav-3-ene or isoflavan structures for the prevention and/or treatment of photoageing in skin subject to UV exposure. Photoageing includes lines, wrinkles, freckles, yellowing of skin, skin stretching, dilated capillaries, cherry red spots and dry complexion.

In another aspect of this invention there is provided use of the compounds of the invention in the prevention and/or treatment of actinic damage. Actinic damage includes solar keratoses or actinic keratoses.

In accordance with another aspect of this invention there is provided a method for the prevention and/or treatment of photoageing in skin subject to UV exposure which comprises administering to a subject a composition containing one or more of equol, dehydroequol, or other isoflav-3-ene, or isoflavan compounds in admixture with one or more acceptable carriers and/or excipients.

In accordance with another aspect of this invention there is provided a method for the prevention and/or treatment of actinic damage which comprises administering to a subject a composition containing one or more of equol, dehydroequol, or other isoflav-3-ene, or isoflavan compounds in admixture with one or more acceptable carriers and/or excipients.

Isoflav-3-ene and isoflavan compounds may be represented by the general formula (II)

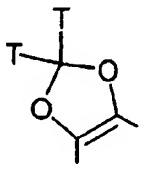


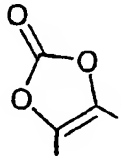
(II)

in which

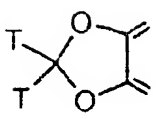
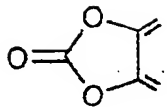
R_1, R_2, R_3 and R_4 are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_{11}R_{12}$, alkyl, haloalkyl, arylalkyl, alkenyl, alkynyl, aryl, heteroaryl, alkylaryl, alkoxyaryl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo, or

R_3 and R_4 are as previously defined, and R_1 and R_2 taken together with the carbon atoms to which they are attached form a five-membered ring selected from

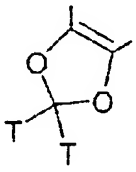
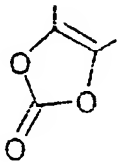




R_1 and R_4 are as previously defined, and R_2 and R_3 taken together with the carbon atoms to which they are attached form a five-membered ring selected from



, or

R_1 and R_2 are as previously defined, and R_3 and R_4 taken together with the carbon atoms to which they are attached form a five-membered ring selected from

and

wherein

R_5, R_6 and R_7 are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_{11}R_{12}$, alkyl, haloalkyl, arylalkyl, alkenyl, alkynyl, aryl, heteroaryl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

R_8 is hydrogen, hydroxy, alkyl, aryl, amino, thio, $NR_{11}R_{12}$, $CONR_{11}R_{12}$, $C(O)R_{13}$ where R_{13} is hydrogen, alkyl, aryl, arylalkyl or an amino acid, or CO_2R_{14} where R_{14} is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{13}$ where R_{13} is as previously defined, or $Si(R_{15})_3$ where each R_{15} is independently hydrogen, alkyl or aryl,

R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,

R_{11} is hydrogen, alkyl, arylalkyl, alkenyl, aryl, an amino acid, $C(O)R_{13}$ where R_{13} is as previously defined, or CO_2R_{14} where R_{14} is as previously defined,

R_{12} is hydrogen, alkyl or aryl, or

R_{11} and R_{12} taken together with the nitrogen to which they are attached comprise pyrrolidinyl or piperidinyl,

the drawing "---" represents either a single bond or a double bond, preferably a double bond,

T is independently hydrogen, alkyl or aryl, and

X is O, NR_{12} or S, preferably O,
including pharmaceutically acceptable salts and derivatives thereof.

Preferably compounds of the formula II are equol and dehydroequol.

Most people, including children, teenagers, adults, and the elderly are exposed to UV exposure and sunlight. Indeed, sunlight provides the principal UV exposure experienced by skin. It is believed that most people would benefit from use of compounds of the present invention.

Compounds of the present invention prevent or treat photoageing and actinic damage. Further, compounds of the present invention promote both the rate and extent of DNA repair and protection in skin.

Compounds according to the present invention may be administered topically, orally or parenterally, or by other modes of administration.

Preferably, compositions containing one or more compounds according to the present invention are applied to the skin either before, at the time of, or after UV or sunlight exposure. For example, compositions may be in the form of a cream, including face cream or skin cream, lotion, cosmetic formulation and the like. For example, compounds of the present invention may be simply mixed, admixed, or blended with suitable carriers or bases to give compositions suitable for application to the skin.

Compounds of the formula II may be generally used in amounts from 20 µg to 500 mg/kg body weight of a subject. Topical compositions may contain compounds of the formula II on a w/w % basis of, for example, 0.01 to 60% w/w, with the remainder comprising carriers and/or excipients and/or standard components used in dermally acceptable compositions as are known in the art.

Compounds of the present invention have preventative and/or treatment applications as described herein. The compounds are preventative in that they lessen, inhibit, or generally prevent photoageing in skin subject to UV exposure and actinic damage. Compounds of the present invention are useful in the treatment of the aforementioned conditions in providing ameliorative outcomes once a subject experiences one or more of the conditions. The compounds of the present invention may be considered as both preventative and as a treatment of the aforementioned conditions in that they prevent or lessen photoageing, or actinic damage, or skin cancers, whilst at the same time treating the condition at hand.

The applicant has found that the compounds according to this invention promote DNA repair. The promotion of DNA repair may be by one or more of increasing the rate of repair of cyclobutane pyrimidine dimers (CPDs), promoting DNA repair by decreasing P53 expression, and/or by promoting the formation of metallothionein (MT). These effects may be responsible for the prevention and/or treatment of skin photoageing and actinic damage through promoting skin health and condition, and preventing skin cell damage.

The formation of CPD is considered to be an important lethal and mutagenic consequence of UVR exposure (Mitchell et al, 1989; Liardet et al, 2000). Animal models have demonstrated an inverse relationship between epidermal CPD repair and skin carcinogenesis (Young et al, 1996). The P53 protein (TP53) is expressed after DNA damage by UV irradiation. P53 is a transcription factor which blocks cellular progression from G1 to S phase, thus preventing replication of damaged DNA (Campbell et al, 1993). The P53 protein may act as a tumour promoting agent (Murphey et al, 2001).

This invention will be described with reference to the following, non-limiting examples.

Example 1

Equol was applied to the skin of five human volunteers immediately after and at 4 hours and 6 hours post-UV irradiation. Twenty-four hours after UV irradiation, MT production was measured. A control lotion was also used containing no equol. This experiment demonstrated that equol caused a statistically significant (P=0.469) elevation in the level of

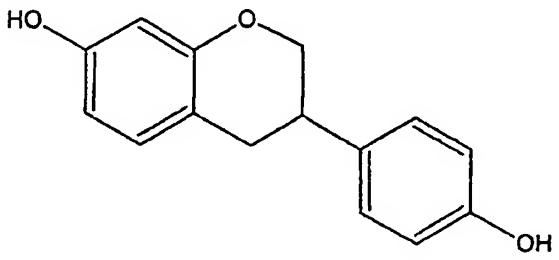
MT in the basal layer of irradiated skin (24 hour post-UV) when compared with unirradiated base line skin (pre-UVR). The vehicle itself did not statistically alter the level of MT in the basal layer of irradiated skin, when compared with unirradiated base line skin.

A reduction in skin wrinkling, capillary dilation and dry skin may also be observed.

Example 2

Cyclobutane Pyrimidine Dimers (CPD):

The formation of CPD's, which occurs immediately on UV exposure (Viv Reeve, *pers comm*) would be unaffected by any therapeutic agent applied post-UVR. However, the rate of repair of CPDs might be increased by equol. If this occurred, fewer CPDs in equol treated skin compared with the number in vehicle-only treated skin would be observed.



Equol (CAS No. 531-95-3)

There were few CPDs in the unirradiated skin of the human volunteer, who demonstrated the expected marked elevation 10 minutes after UV exposure. The human subject treated demonstrated a lower percentage of CPD+ve epidermal cells in equol treated skin.

Lower levels of CPD may be associated with preventing and/or treating lines, wrinkles, freckles, yellowing of skin, stretching of skin, dilated capillaries, cherry red spots, dry complexion, solar keratoses or actinic keratoses.

Example 3

Hairless mice treated with equol or dehydroequol either before or after chronic UV

exposure show decreased skin thickness than non-treated mice. Increased skin thickness may be associated with wrinkles, capillary dilation in skin and skin dryness, as well as actinic damage.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia.

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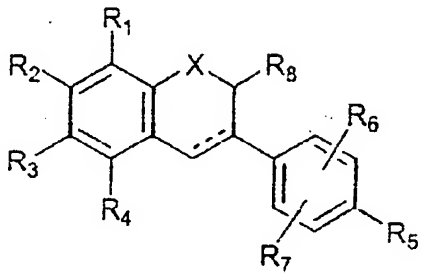
Claims

1. Use of compounds of the formula II for the prevention and/or treatment of skin photoageing or actinic damage of skin associated with UV exposure, wherein said compounds of the formula II comprise

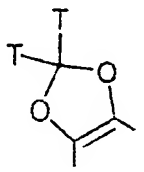


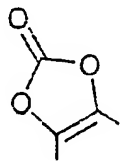
(II)

in which

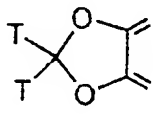
R_1, R_2, R_3 and R_4 are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_{11}R_{12}$, alkyl, haloalkyl, arylalkyl, alkenyl, alkynyl, aryl, heteroaryl, alkylaryl, alkoxyaryl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo, or

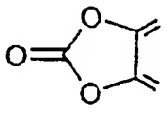
R_3 and R_4 are as previously defined, and R_1 and R_2 taken together with the carbon atoms to which they are attached form a five-membered ring selected from





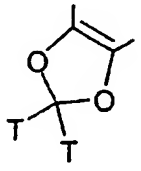
R_1 and R_4 are as previously defined, and R_2 and R_3 taken together with the carbon atoms to which they are attached form a five-membered ring selected from

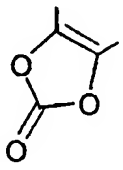




, or

R_1 and R_2 are as previously defined, and R_3 and R_4 taken together with the carbon atoms to which they are attached form a five-membered ring selected from





and

wherein

R_5, R_6 and R_7 are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_{11}R_{12}$, alkyl, haloalkyl, arylalkyl, alkenyl, alkynyl, aryl, heteroaryl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

R_8 is hydrogen, hydroxy, alkyl, aryl, amino, thio, $NR_{11}R_{12}$, $CONR_{11}R_{12}$, $C(O)R_{13}$ where R_{13} is hydrogen, alkyl, aryl, arylalkyl or an amino acid, or CO_2R_{14} where R_{14} is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{13}$ where R_{13} is as previously defined, or $Si(R_{15})_3$ where each R_{15} is independently hydrogen, alkyl or aryl,

R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,

R_{11} is hydrogen, alkyl, arylalkyl, alkenyl, aryl, an amino acid, $C(O)R_{13}$ where R_{13} is as previously defined, or CO_2R_{14} where R_{14} is as previously defined,

R_{12} is hydrogen, alkyl or aryl, or

R_{11} and R_{12} taken together with the nitrogen to which they are attached comprise pyrrolidinyl or piperidinyl,

the drawing "---" represents either a single bond or a double bond, preferably a double bond,

T is independently hydrogen, alkyl or aryl, and

X is O, NR_{12} or S, preferably O,

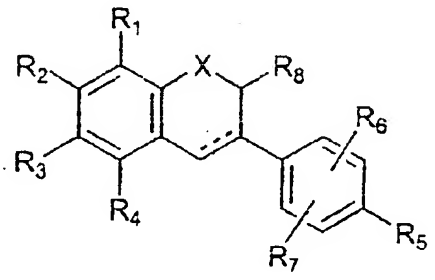
including pharmaceutically acceptable salts and derivatives thereof.

2. Use according to claim 1 for the prevention and/or treatment of skin photoageing selected from lines, wrinkles, freckles, yellowing of skin, skin stretching, dilated capillaries, cherry red spots and dry complexion.

3. Use according to claim 1 for the prevention and/or treatment of actinic damage selected from solar keratoses or actinic keratoses.

4. Use according to claim 1 wherein said compounds of the formula (II) comprise equol or dehydroequol.

5. A method for the prevention and/or treatment of skin photoageing or actinic damage of skin which comprises administering to a subject one or more compounds of the general formula (II)

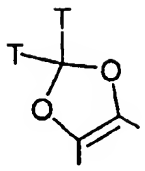
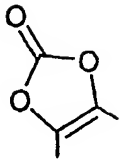


(II)

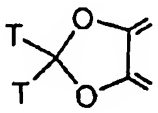
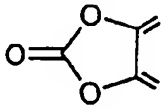
in which

R_1, R_2, R_3 and R_4 are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_{11}R_{12}$, alkyl, haloalkyl, arylalkyl, alkenyl, alkynyl, aryl, heteroaryl, alkylaryl, alkoxyaryl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo, or

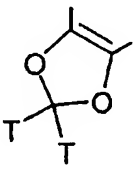
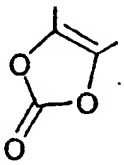
R_3 and R_4 are as previously defined, and R_1 and R_2 taken together with the carbon atoms to which they are attached form a five-membered ring selected from

R_1 and R_4 are as previously defined, and R_2 and R_3 taken together with the carbon atoms to which they are attached form a five-membered ring selected from



, or

R_1 and R_2 are as previously defined, and R_3 and R_4 taken together with the carbon atoms to which they are attached form a five-membered ring selected from

and

wherein

R_5, R_6 and R_7 are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_{11}R_{12}$, alkyl, haloalkyl, arylalkyl, alkenyl, alkynyl, aryl, heteroaryl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

R_8 is hydrogen, hydroxy, alkyl, aryl, amino, thio, $NR_{11}R_{12}$, $CONR_{11}R_{12}$, $C(O)R_{13}$ where R_{13} is hydrogen, alkyl, aryl, arylalkyl or an amino acid, or CO_2R_{14} where R_{14} is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{13}$ where R_{13} is as previously defined, or $Si(R_{15})_3$ where each R_{15} is independently hydrogen, alkyl or aryl,

R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,

R_{11} is hydrogen, alkyl, arylalkyl, alkenyl, aryl, an amino acid, $C(O)R_{13}$ where R_{13} is as previously defined, or CO_2R_{14} where R_{14} is as previously defined,

R_{12} is hydrogen, alkyl or aryl, or

R_{11} and R_{12} taken together with the nitrogen to which they are attached comprise pyrrolidinyl or piperidinyl,

the drawing "---" represents either a single bond or a double bond, preferably a double bond,

T is independently hydrogen, alkyl or aryl, and

X is O, NR_{12} or S, preferably O,

including pharmaceutically acceptable salts and derivatives thereof.

6. A method according to claim 5 wherein said one or more compounds of the formula (II) comprises equol and dehydroequol.

7. A method according to claim 5 which is a method for the prevention and/or treatment of skin photoageing selected from lines, wrinkles, freckles, yellowing of skin, skin stretching, dilated capillaries, cherry red spots and dry complexion.

8. A method according to claim 5 which is a method for the prevention and/or treatment of actinic damage selected from solar keratoses or actinic keratoses.

9. A method according to claim 5 wherein said one or more compounds of the formula (II) are administered orally, parenterally or topically, before and/or after skin exposure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2003/001265

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61K 7/48, 31/12, 31/35, 31/40, 31/475

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DWPI, Medline, Chemical Abstracts and keywords: isoflav, equol, UV, Ultra Violet, skin, DNA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Widyarini S. *et al.*, 'Isoflavonoid Compounds from Red Clover (*Trifolium pratense*) Protect from Inflammation and Immune Suppression Induced by UV Radiation', *Photochemistry and Photobiology*, Vol 74, No 3, 2001, pages 465-470. Abstract.	1-9
X	WO 99/36050 (NOVOGEN RESEARCH PTY LTD) 22 July 1999 Page 2 lines 10-12, page 3 lines25-31, page 12 lines22-26, page 16 example 2 and page 18 example 3.	1-9
X	WO 98/08503 (NOVOGEN RESEARCH PTY LTD) 5 March 1998 Page 6 lines 19-20, page 18 example 1 compound 10 and page 28 synthesis 5.	1-9

☐ Further documents are listed in the continuation of Box C ☒ See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 October 2003	5 NOV 2003
Name and mailing address of the ISA/AU	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2003/001265

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	9936050	AU	16518/99	CA	2316349	EP	1049451
		NO	20003201	NZ	505377	SE	0002286
		US	6455032	US	2003059384		
WO	9808503	AU	40034/97	BR	9713180	CN	1233173
		EP	0954302	GB	2331015	HK	1019553
		HU	9903971	NO	990965	NZ	334025
		US	2002198248	US	2003018060		

END OF ANNEX